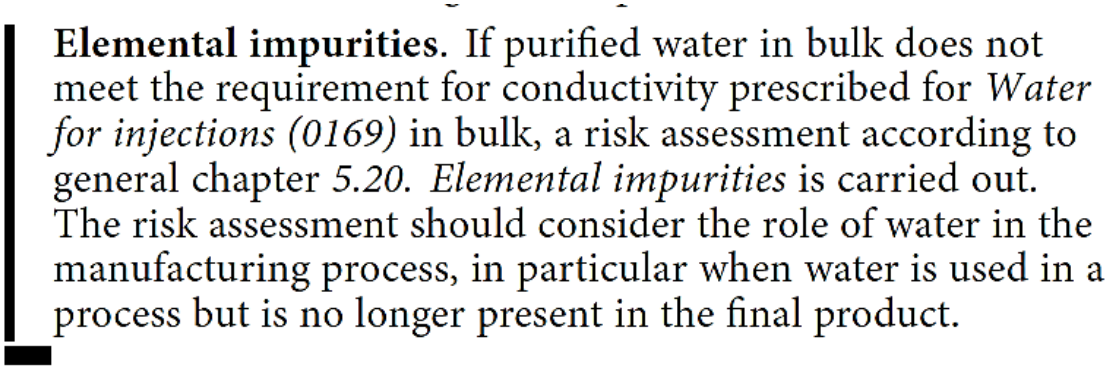
Risk assessment of Elemental Impurities in Purified Water: Compliance with European Pharmacopoeia 9.4

Daniel Martín, Ignacio Jorge & Paulino Alonso

1 INTRODUCTION

The European Pharmacopoeia updated the monograph 04/2018:0008 to align the requirement of elemental impurities with ICH Q3D:

Heavy metal test is removed from EP monograph and a new section is included: **Elemental impurities**. *"If purified water in bulk does not meet the requirement for conductivity prescribed for Water for injections (0169) in bulk, a risk assessment according to general chapter 5.20 Elemental impurities is carried out. The risk assessment should consider the role of water in the manufacturing process, in particular when water is used in a process but is no longer present in the final product."*


Elemental impurities. If purified water in bulk does not meet the requirement for conductivity prescribed for *Water for injections (0169)* in bulk, a risk assessment according to general chapter *5.20. Elemental impurities* is carried out. The risk assessment should consider the role of water in the manufacturing process, in particular when water is used in a process but is no longer present in the final product.

Screenshot extracted from European Pharmacopeia 9.4, Purified Water monograph

This update does not mean that Purified Water in bulk should comply with the conductivity of Water for Injection. It means that the risk assessment might be avoided if you are capable of complying/reducing the conductivity in your PW to the levels of WFI.

What are the **Consequences** of this update?

1. If you are using Water for Injection: further assessment is not necessary.
2. If you are using Purified Water and its possible to demonstrate your conductivity levels consistently achieve WFI specifications: further assessment is not necessary, however conductivity excursions need assessment!
3. If you are using Purified Water and your water conductivity specifications are typically above WFI specifications: risk assessment is necessary.

In this document it will be explained how to perform this risk assessment.

2 RISK ASSESSMENT PRINCIPLES

A risk assessment according to ICH Q3D and *General Chapter 5.20* should include information regarding the following points:

a) Materials of construction and materials in contact with the PW: what are the materials in contact with PW in the generation plant and in the PW loop? Are they suitable for PW production and distribution?
b) Maintenance and qualification: Is the PW loop qualified and appropriately maintained according to preventive maintenance programs and GMP (e.g. sanitization, passivation, etc.)?
c) PW generation: How is the PW produced? Can the process potentially introduce or remove elemental impurities? What is the quality of the starting water (e.g. drinking water)? Are there implemented any pre-treatment to the starting water before feeding the PW generation system?
d) Controls: How is the quality of starting water? How is controlled the PW, frequency, sampling, and conductivity specifications?

Conductivity controls: conductivity is intrinsically related with the presence of ions in the water and thus with elemental impurities content. Hence, it is very important to perform conductivity controls in the loop and/or generator and/or points of use, continuously or daily. The EP PW monograph correlates conductivity directly with the risk of inclusion of elemental impurities.

Conductivities in PW below WFI conductivity specifications (e.g.: 1.3 $\mu S*cm^{-1}$ at 25ºC) are exempt of further considerations: Risk is considered consistently controlled and EI inclusion is sufficiently reduced.

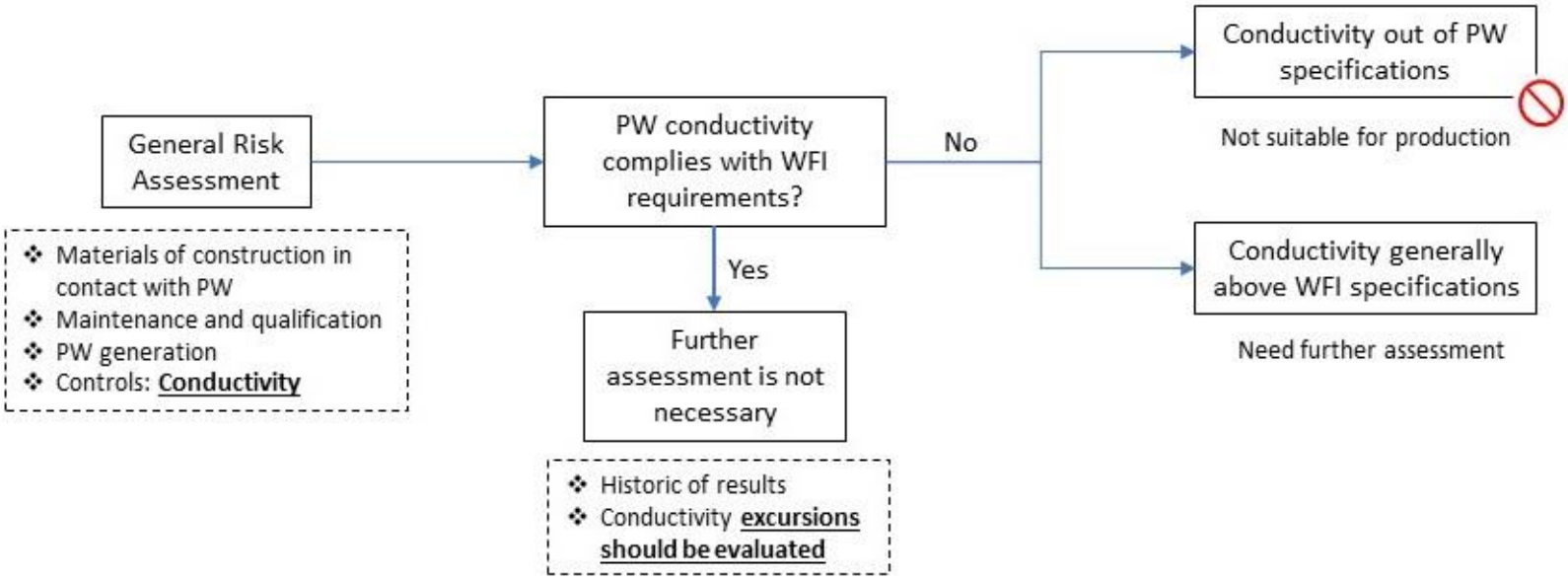
Therefore, it is possible to differentiate 3 scenarios:

1. Conductivities consistently below 1.3 $\mu S*cm^{-1}$ at 25ºC do not need further assessment, however, conductivity excursions should be investigated.
2. Conductivities above 1.3 $\mu S*cm^{-1}$ at 25ºC need further assessment.
3. Conductivities above 5.1 $\mu S*cm^{-1}$ at 25ºC are not suitable for production

Table 1. Relevant conductivity-temperature requirements for PW and WFI according to EP.

Purified Water		**Water for Injection**	
Temperature (ºC)	Conductivity ($\mu S*cm^{-1}$)	Temperature (ºC)	Conductivity ($\mu S*cm^{-1}$)
20	4.3	20	1.1
25	5.1	25	1.3
30	5.4	30	1.4
80	9.7	80	2.7
90	9.7	90	2.7

Flowchart of Risk Assessment Principles.



3 RISK ASSESSMENT STRATEGY

3.1 PW conductivity complies with WFI values

- Document the risk assessment: Historic of results that permit to understand this result is achieved and maintained through the principles described above.
- You should keep monitoring the conductivity values.
- Conductivity excursions (e.g. above 1.3 µS*cm^{-1} at 25ºC) should be investigated. It is recommended to set a procedure to inform the responsible departments when this happens.
- The investigation could include the screening of all 24 EIs. This is highly recommended to cover 100% the assessment. However, the screening could also target only potentially present EIs (review of the materials of construction following ICH Q3D recommendations).
- The screening should be done by an appropriate technique (e.g. ICP-MS). This would help to generate further data and knowledge of the potential risk and presence of elemental impurities in your PW.
- The screening preferably would target the lowest possible detection limits (LoQ and/or LoD) for each elemental impurity (ppb orders at least). Depending on the results obtained, further evaluation and risk assessment may be required.

3.2 PW conductivities are generally above the limits established for WFI

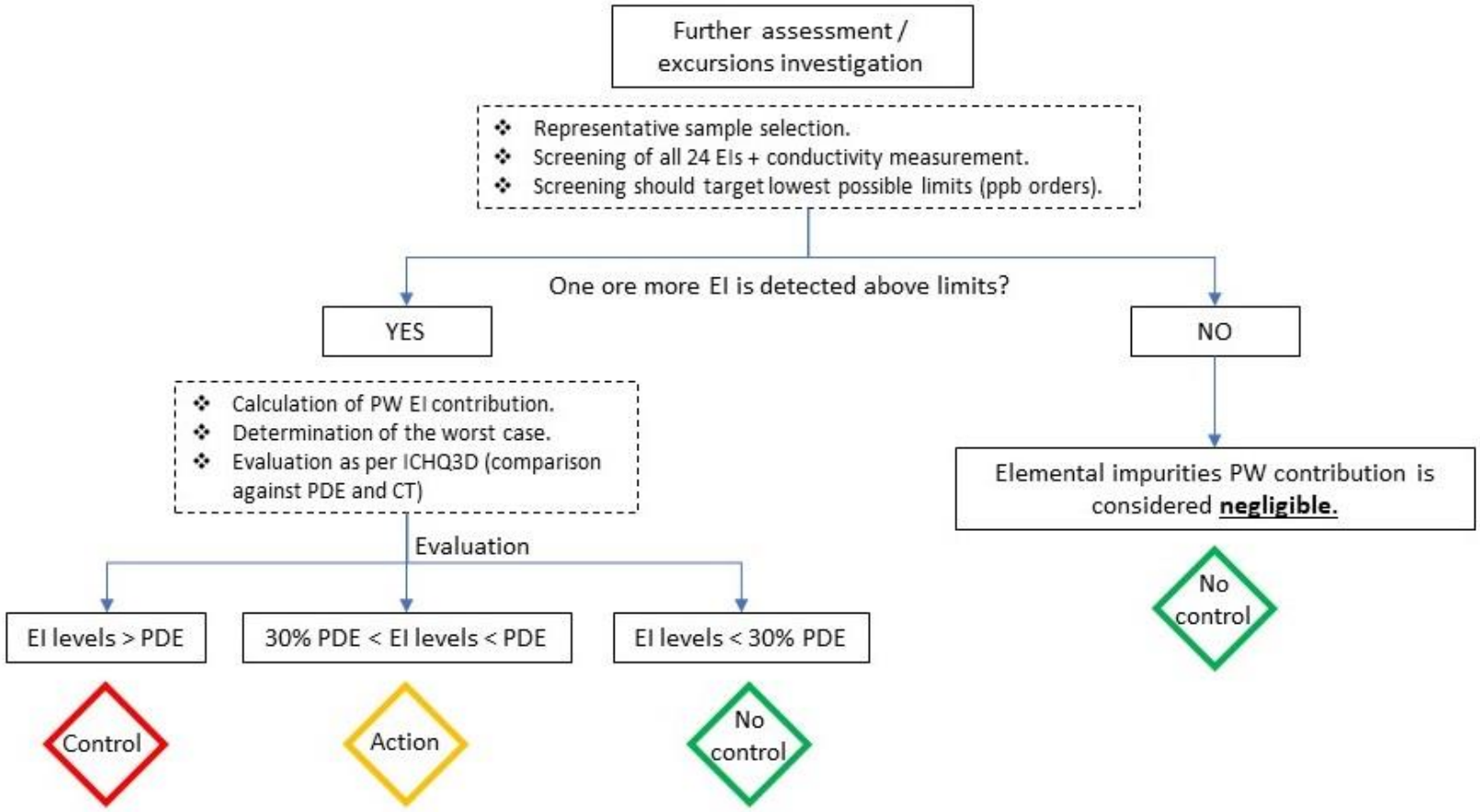
- A risk assessment is required: it should aim to correlate conductivity levels with concentration of elemental impurities.
- A screening of all 24 elemental impurities should be performed. This is highly recommended to cover 100% the assessment. However, the screening could also target only potentially present EIs (review of the materials of construction following ICH Q3D recommendations).
- The screening should be done by an appropriate technique by an appropriate method (ICP-MS) should be performed in at least 3 representative samples of PW, covering the potential variability. The selection criteria of the samples can include but is not limited to: different days, different point of use, worst-case points of use, etc.
- The conductivity of the selected samples of PW should also be measured for comparison with elemental analysis results.
- The screening preferably would target the lowest possible detection limits (LoQ and/or LoD) for each elemental impurity. Depending on the results obtained, further evaluation and risk assessment may be required.
- If the LoQ/LoD are sufficiently low (i.e. <0.75 µg/L) and no elemental impurities are detected above the LoQ or LoD, the **risk would be considered negligible.**
- This exercise of risk assessment should be repeated with an appropriate frequency and/or when major changes affect the PW loop/generator.

Elemental Impurities detected in the analysis of the water.

- One or more elemental impurities are detected in the screening
- Then the next step would be to evaluate the impact in all your products: worst-case approach could facilitate this task.

- It would therefore be necessary to define and determine what is (or are) the product(s) that represent the worst-case(s) (see below).
- A risk evaluation according to ICH Q3D principles would determine if:
    a) The observed elemental impurities represent a negligible risk (overall contribution <30% of PDE).
    b) You need to implement actions that guarantee that the PDE limit is not exceeded (30%PDE < overall contribution < PDE).
    c) You need to adopt control strategies that reduce the concentration of the observed element (overall contribution >PDE).

Flowchart of Risk Assessment Strategy.



4 WORST-CASE SELECTION, DETERMINATION OF ACCEPTABLE LIMITS, EVALUATION AND VERIFICATION.

To determine the potential impact of the presence of an observed elemental impurity in your products there are two options:

a) Evaluate the impact according to ICH Q3D in each product (in other words, consider the contribution of PW in the risk assessment of each finished drug product).

b) Evaluate the overall impact considering the worst-case scenario.

Note that primary evaluation based on the worst-case approach is highly recommended in manufacturing sites which produces multiple products that uses PW.

Determination of the worst-case(s):

In order to determine the worst-case scenario should be considered what is the maximum impact of finding a certain element in PW. The first recommendation is to classify the products depending on the use of the water:

a) Products in which Purified Water is an excipient
b) Products in which Purified Water is a service (eliminated during process)

a) Products in which PW is an excipient: the worst case would be represented by the patients taking more PW per day. Translated to a manufacturing site, this is represented by the combination of product with a highest amount of PW in the composition and the highest maximum daily intake. For example:

Syrup A contains 20 mL of PW per unit dose; maximum daily intake 1 dose per day; Syrup B contains 15 mL of PW per unit dose; maximum daily intake 2 doses per day → The worst case would be Syrup B (30 mL/day); or if your data matrix is too complicated, the 'combined worst-case' would be 20 mL*2 doses = 40 mL/day.

b) Products in which PW is used in the manufacturing process but evaporated afterwards: it is removed during the manufacturing process and hence is no longer present in the product. The worst case would be represented by the formulation in which more purified water is used per unit dose combined with the maximum doses per day. For example:

Tablets A are manufactured with 400 kg of PW per 1,000,000 tablets (batch size); Tablets B are manufactured with 300 kg of PW per 500,000 tablets; the worst-case would be 'Tablets B' with 300 kg/500,000 unit dose = 0.6 g/tablet. In addition, the dosing schedule of Tablets A is 4 tablets per day, whereas the dosing schedule of Tablets B is 1 tablet per day, thus, in this example, the worst-case in terms of posology would be 4 doses/day. The 'combined worst-case' would be 300 kg /500,000 tablets * 4 tablets/day = 2.4 g/day

Evaluation as per ICH Q3D in the worst-case scenario: Definition of Acceptable Limits

According to ICH Q3D, there are established PDE values for all the 24 elemental impurities for the oral, the parenteral and the inhaled routes of administration. These values should be taken for the definition of the acceptable limits (see ICH Q3D guideline).

The acceptable limit could be established as per ICH Q3D by the following approach:

1) Calculate the acceptable limit of elemental impurities that could be attributed to purified water according to your worst-case (or for each product, as detailed above) as follows:

Acceptable Limit (µg/g or µg/mL) = established PDE (µg/day)/worst-case scenario (g/day or mL/day)

2) Compare the experimental result with the acceptable limit: depending on this comparison, you would conclude the following:

Result of the evaluation		
PW contribution <30% of PDE	**No control**	Contribution of PW would be considered **negligible.** Nevertheless, conductivity needs monitoring.
30% PDE <PW contribution <100% PDE	**Action***	Actions may be put in place to keep the content of the elemental impurity detected under acceptable limits
PW contribution >100% PDE	**Control***	A control strategy should be planned for reducing the content and/or potential impact of the elemental impurity detected.

**Noted that if the worst-case scenario is considered for calculations the result may exaggerate the impact. In this case, the recommendation would be to evaluate the impact in each product.*

Verification step

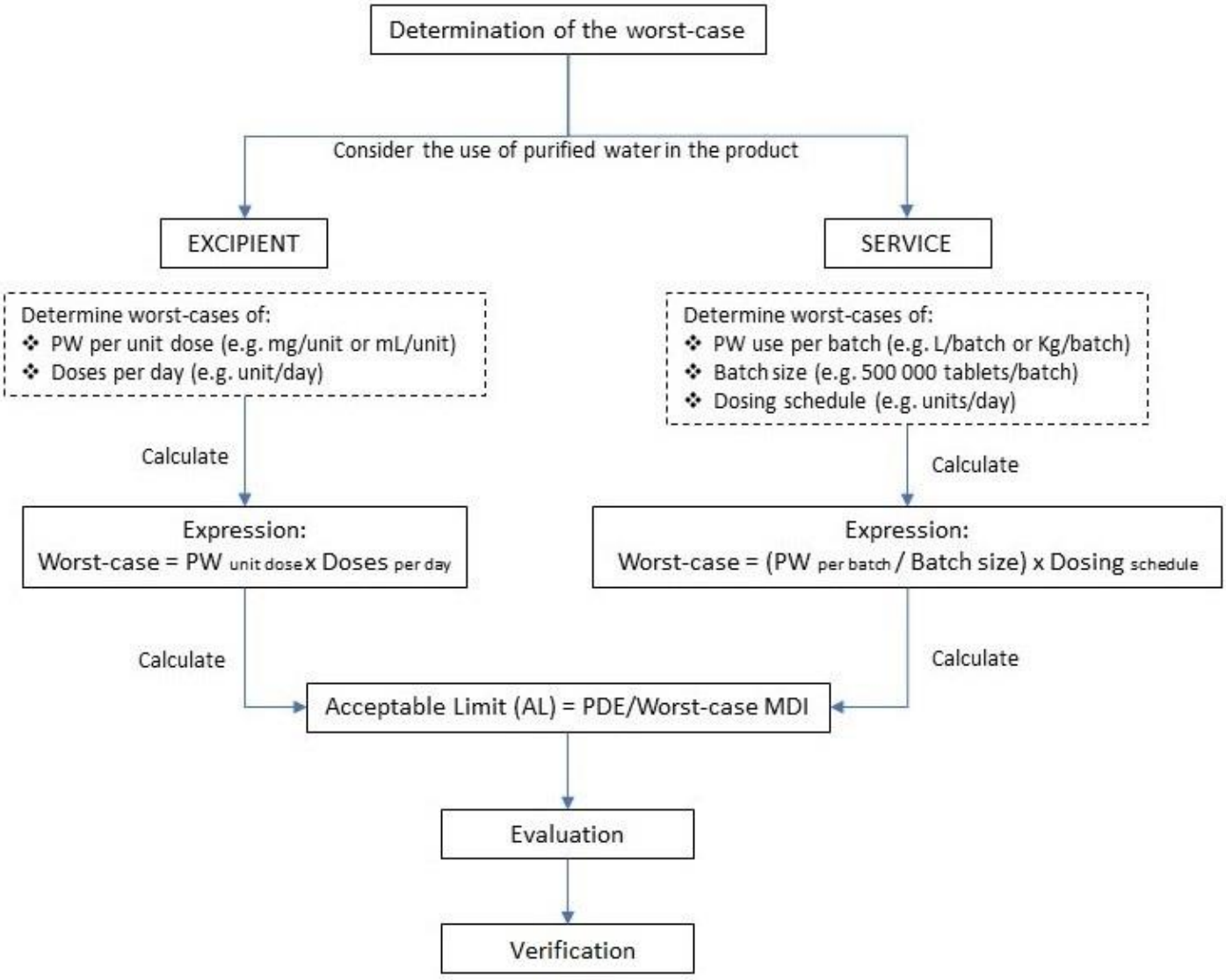
ICH Q3D is focused on elemental impurities in the finished drug product, and therefore the contribution of PW should be evaluated in an overall risk assessment. This is necessary to take into consideration the potential contribution of elemental impurities from other sources (e.g. API, excipients, etc.).

After all this would require assessing the potential impact in each drug product. However, in the meantime, this GAP could be covered by the verification of the potential impact of the observed result in the product in which the maximum daily intake of the elemental impurity is higher.

Example:

Product A + Product B have been selected for the worst case as described above; the result is below the acceptable limit. However, Product C shows a maximum daily intake of Nickel of 30 µg/day. The contribution of another 20 µg/day would sum up to 50 µg/day. The result is still below 60 µg/day (30% of the established PDE). and in this case your 'worst-case scenario approach' would have been verified, and you could conclude that the result of nickel in your PW does not significantly impact in your products.

Flowchart of Worst-Case Selection, Determination of Acceptable Limits, Evaluation and Verification.



General flowchart